## REMARKS

Reconsideration is requested.

The specification has been revised to include the attached Sequence Listing and corresponding sequence identifiers in response to the Notice to Comply dated July 22, 2008. The attached paper and computer readable copies of the Sequence Listing are the same. No new matter has been added. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in response to the Notice to Comply.

In claim 1, the phrase 'target molecule of a compound' has been revised above, without prejudice, to refer to 'specific interaction partner of a compound'. Basis for this can be found on page 9, lines 19-24 and page 5, lines 21-23 of the substitute specification filed February 22, 2008:

> "The term 'stably interacts' refers to the interaction between a compound (e. g. a drug or drug derivative) added to a complex mixture of molecules (e. g. a complex protein mixture or a protein peptide mixture). Said interaction is strong enough for the isolation of a partner for said compound, in other words a target molecule for said compound."
>
> "The binding of a compound to the target is specific, meaning that said compound binds to at least one molecule in a complex mixture of molecules and not to other molecules."

For reasons of consistency, the term 'target molecule' has been replaced with 'interaction partner' wherever present in the claims.

Claim 1 has also been revised, without prejudice, to recite two-parts by adding 'characterized in that' after 'a compound', to further define the patentable subject matter.

Claim 1 has been amended to include a list with the three functionalities of the compound. Support for this can be found on page 6, lines 10-14 of the substitute specification filed February 22, 2008:

> "In most general terms, the compound consists of (1) a chemical structure determining the specific interaction between said compound and its target molecule (the"S"-part), (2) a chemically reactive group by which the compound and its target can be tightly cross-linked (the"L"-part) and (3) a functional group which can be altered on a specific and controllable manner (the"A"-part)."

The specific terminology used to refer to the "L"-part is found on page 7, lines 10-11of the substitute specificaiton filed February 22, 2008:

> "The compound also contains a chemically reactive group ("L"-part) which reacts with a functionality present in the target protein."

With regard to the "A"-part, the claim language has been modified to more properly reflect the terminology used in chromatography. Basis is found on page 8, lines 28-30 of the substitute specification filed February 22, 2008:

> "The term "migrates differently" means that a particular altered compound-target complex elutes at a different elution time in run 2 with respect to the elution time of the same non-altered compound-target complex in run 1."

Further, in claim 1 the phrase 'containing 100 or more different molecules' has been added after 'complex mixture of molecules'. Support can be found on page 23, discussing complex protein mixtures, in particular lines 30-32 of the substitute specification filed February 22, 2008:

> "The proteome will be a complex mixture of proteins, generally having at least about 20 different proteins, usually at least about 50 different proteins and in most cases 100 different proteins or more."

The claims have also been revised, without prejudice, to indicate that the molecules with which the compound stably interacts in step (a) is a target molecule or interaction partner. See above-noted passages of specification.

In step (b) of claim 1, the term 'found' has been amended to 'present' for consistency with the wording of step (c).

In step (c) of claim 1, the words 'in each fraction' have been brought forward. While normally each fraction will be treated to alter the compounds present (see e.g. Examples 1.5 and 1.6 (pages 31-36 of the substitute specification filed February 22, 2008), the compound-interaction partner complex will only be present in the fraction wherein the interaction partner is present (cf. e.g. Example 1.5 and Figure 1A and 1B and Example 1.6 and Figures 3A and 3B).

For purposes of uniformity, all dependent claims have been amended to start with "The method according to claim…".

The claim dependency of claim 5 has been revised to be dependent from claim 1.

The term 'protein mixture' in claim 3 has been revised to 'mixture of proteins' for antecedent basis. Similarly, in claim 5, 'the targets' has been replaced with 'the at least one interaction partner'. The phrases and terms 'target molecules', 'proteins' and 'peptides' in claims 6 and 7 have been revised to read 'at least one interaction partner', 'at least one protein' or 'at least one peptide', respectively.

The list in claim 6 has been replaced by the term "a mass spectrometric approach". Support for this is found on page 15 of the application, lines 16-17:

> "In a particular embodiment the identification of the targets can be carried out by a mass spectrometric approach."

In claim 7, the list on which the measurement of the peptides is combined in the identifying step has been replaced, without prejudice, with "based on the mass of the altered compound". Basis for this amendment can be found on page 16, lines 5-9:

> "The information obtained is primarily the mass of the tagged peptide(s). This mass is the sum of the mass of the peptide and the mass of the tag (the altered compound component). Since the latter mass is known from the alteration reaction, this tag mass can be subtracted from the total mass of the tagged peptide resulting in a peptide mass which will be the basis in further searching algorithms."

New claims 8 and 9 have been added. Claim 8 is directed to the particular case where the compound used is a drug. Support for this claim can be found on page 6, lines 6-8:

> "'Compounds' comprise small compounds (organic or inorganic), existing drugs, drugs in development, drug leads, drug analogues or drug derivatives."

Claim 9 relates to the possibility of pooling the fractions. Support for the claim is found e.g. on page 13, line 11 – page 13, line 21, and in Example 1.6, particularly also Table 1.

No new matter has been added. Entry of the present Amendment is requested.

The objections to claims 3 and 5-7 are obviated by the above amendments. Entry of the present Amendment and withdrawal of the objections are requested.

The Section 112, second paragraph, rejection of claims 1-7, is obviated by the above amendments. Entry of the present Amendment and withdrawal of the rejection is requested.

To the extent not obviated by the above amendments, the Section 102 rejections of claims 1 and 5 over Cruickshank (Canadian Journal of Biochemistry (1974) 52, 1013-17), and of claims 1, 2 and 4 over Creighton ("Proteins: Structure and Molecular Properties" Second Edition, W.H. Freeman and Company, New York, 1993, page 41), are traversed. Reconsideration and withdrawal of the rejections are requested in view of the above and the following distinguishing comments.

Without acquiescence to this rejection, the applicants note that claim 1, as amended above, explicitly refers to the fact that the compound is added to a complex mixture of molecules, containing 100 or more different molecules. The same is true for claim 5 (which depends on claim 1). The Cruickshank reference is understood to deal with analysis of a single protein (chymotrypsinogen) and not with analysis of complex mixtures. The cited reference therefore fails to teach each and every aspect of the claimed invention Cruickshank et al. fails to anticipate claims 1 or 5. Moreover, the FDNB compound disclosed in Cruickshank et al. is not a compound according to the revised claim 1, as it for instance does not have a specificity-determining part (“S”-part). This feature is nowhere disclosed or suggested in Cruickshank et al., but is required by the amended claims. Cruickshank et al. does not anticipate claim 1 or 5.

Like Cruickshank et al., Creighton deals with a single protein. For this reason alone, the rejection of claim 2 (referring to a mixture of proteins) should be withdrawn.

Claim 1 as currently amended specifies that the complex mixtures in the claim language contain more than 100 different molecules, a feature which is not described or suggested by the Creighton reference. Moreover, Creighton also does not disclose compounds with a specificity-determining part. The cited art therefore fails to teach each and every aspect of the claimed invention, either expressly or inherently. Therefore, Creighton et al. cannot be said to anticipate any of claims 1, 2 and 4.

Entry of the present Amendment and withdrawal of the Section 102 rejections are requested.

To the extent not obviated by the above amendments, the Section 103 rejections of claims 2-4 over Cruickshank, and of claims 2, 3, 4, 6 and 7 over Cruickshank and Aebersold (U.S. Patent No. 6,670,194) and Johansson (U.S. Patent No. 6,716,589), and of claims 2, 3 and 5-7 over Creighton in view of Aebersold, are traversed. Reconsideration and withdrawal of the rejections are requested in view of the above and the following distinguishing comments.

The applicants note the Examiner has not rejected independent claim 1 as allegedly having been obvious, but rather only rejected dependent claims as allegedly having been obvious.

The Examiner is understood to believe that Cruickshank teaches contacting a compound with a complex mixture of molecules. As explained above however, Cruickshank et al. fails to teach or suggest using a complex mixture of molecules, containing 100 or more different molecules. Moreover, the different functionalities of the

compound, particularly the specificity-determining part are not disclosed or suggested by Cruickshank.

The applicants are uncertain as to how a reference describing a method for a single protein would have, by itself, render an invention dealing with complex mixtures (e.g. entire proteomes) obvious, nor why an ordinarily skilled person would have been motivated to work with a compound comprising three functionalities, as there is no teaching or suggestion to this end in Cruickshank et al. Reconsideration and withdrawal of the Section 103 rejection are requested. Clarification from the Examiner is requested in the event the rejection is maintained as to how Cruickshank et al., by itself, would have made it obvious to adapt the method disclosed for the analysis of mixtures of more than 100 different molecules, while at the same time using a compound with three functionalities, which is not suggested in the publication of Cruickshank et al. Withdrawal of the Section 103 rejection is requested.

As for the Examiner's combinations of Cruickshank et al. in view of Aebersold et al. and in view of Johansson et al., the rejections are understood to be based on the assumption that a person of ordinary skill in the art at the time of the instant invention could have performed the method of Cruickshank et al. using a complex mixture of proteins, as taught by Aebersold et al., rather than a single protein. In this regard, reference is made to 'complex mixtures of proteins' described in Aebersold and the teaching of 'multiplexing', the analysis of multiple samples in a single analysis. The applicants previous remarks that one of ordinary skill in the art would not have combined the reference teachings because Cruickshank works with one protein while

Aebersold et al. work with more than one protein but does not use two identical chromatographic steps was deemed not persuasive because it allegedly amounted to a piecemeal analysis of the prior art teachings, and the test should be what the combined teachings of the references would have suggested to those of ordinary skill in the art.

The applicants maintains that an ordinarily skilled person would not have combined the two references, and even if he had combined them, this combination would not have resulted in the instantly claimed invention.

First of all, the present application is concerned with the isolation and identification of specific interaction partners of compounds, e.g. the specific molecules targeted by a drug. See e.g. the title of the application and page 2, lines 13-26. Even the site on the molecule can be identified using the present method. Cruickshank et al. is a paper about purification of tyrosyl peptides of a protein (see title and “Results” section on page 1015), while the Aebersold patent relates to rapid quantitative analysis of proteins (see title and e.g. column 3, lines 8-24). Neither document mentions or suggests the identification of an (unknown) interaction partner of a compound, indeed both documents relate to purification or quantification of given proteins, i.e. of which at least something is known (tyrosyl peptides in Cruickshank, ‘specific proteins’ or ‘a given protein or protein function’ in Aebersold (column 3, lines 31-33 and 40-43 respectively)). Thus, a person of ordinary skill in the art, confronted with the problem of how to isolate a specific interaction partner of a compound would not have started from either of the cited references, as they deal with a different problem, and would certainly not combine the two references, as they still do not address this problem, let alone solve it.

However, for the sake of the argument only, it will be shown that even if the references were to be combined, this still would not result in the instantly claimed invention. Cruickshank et al. does not relate to interaction partner identification, the authors work with one protein instead of a complex mixture, and the nature of the compound used differs. Regarding Aebersold, it is stated in the Office Action that

> "Aebersold et al. [disclose] mass spectrometry-based methods for characterizing isolated peptides. The reference teaches analysis of complex mixtures of proteins, i.e., those containing 5 or more distinct proteins or protein functions, digesting the protein sample with proteases to produce peptide fragments." (page 10 of the Office Action dated July 22, 2008, 2nd paragraph, references omitted)

It is noted that, although Aebersold et al. may mention complex mixtures of proteins, this term is defined as "containing 5 or more distinct proteins or protein functions" (column 3, lines 44-45). The example of multiplexing referred to in the Office Action (Table 2 (page 11 of the Office Action, first two lines)) relates to the analysis of a mixture of six known proteins (column 13, line 66 – column 14, line 7).

The applicants submit that this is far from identical to 'containing 100 or more different molecules', as the term is defined in the currently presented claims. Nevertheless, for the sake of the argument herein only, Aebersold will be considered to apply also to complex mixtures containing 100 or more different molecules.

The Office Action states further that Aebersold discloses that

> 'by isolating and analyzing the isolated peptide fragments, the presence of proteins in the sample can be determined' (page 10, 2nd paragraph).

While this may be true, detecting the presence of proteins is not the same as detecting interaction partners of compounds, thereby intentionally discriminating between molecules that specifically interact with the compound and molecules that do not.

The methods of the claimed invention therefore are of a different purpose from those of the cited art, and therefore produce a different result as they envisage different goals to be achieved. Protein quantification of a sample is not the same as isolating specific molecules, which selectively interact with the compound of interest. The affinity labeled reagent disclosed by Aebersold et al. is designed to react with peptides of each protein in a mixture in order to allow protein quantitation and identification for the whole sample (e.g. column 3, lines 9-15; column 5, lines 55-60; column 15, lines 54-57). To achieve this, the reagent should be able to react with peptides derived from each protein. Proteins that do not react with a particular reagent may still be targeted by including reactivity to other groups, as described in column 16, lines 45-52 of the Aebersold patent:

> "The method can be extended to include reactivity toward other functional groups. A small percentage of proteins (8% for S. cerevisiae) contain no cysteinyl residues and are therefore missed by analysis using reagents with sulfhydryl group specificity (i.e., thiol group specificity). Affinity tagged reagents with specificities toward functional groups other than sulfhydryl groups will also make cysteine-free proteins susceptible to analysis."

Thus, even though the reagent reacts with 92% of the proteins present in the mixture, it is still desirable to increase this coverage because otherwise the proteins are 'missed by analysis'.

This is not only different from what is taught in the present application, but a clear teaching away of the instant invention. On page 12, lines 7-10, the present application states:

> "Thus in case of a complex mixture of peptides (e. g. a protein peptide mixture) in which the compound is only linked to one target peptide or to a limited number of target peptides, while the vast majority of peptides is not conjugated to the compound, then the sorting process is as follows." (emphasis added)

If, as is alleged in the Office Action, one would have combined the teachings of Cruickshank et al. with the use of a complex mixture of proteins as allegedly taught by Aebersold et al., one would also learn that it is desirable to react with peptides derived from each protein in the sample in order to allow protein quantitation and identification for the whole sample. Thus, one would not have arrived at the claimed invention wherein only reaction with specific interaction partners of the compound is envisaged. On the contrary, compounds which only react with one or a limited number of molecules would not be suitable for applying the teachings of Aebersold and an ordinarily skilled person would not have used them based on the teachings of Cruickshank et al. combined with Aebersold et al. Consequently, the ordinarily skilled person would not have arrived at the instantly claimed invention.

This is further illustrated by the specific compounds used in the methods of the present application, which have three different functionalities (see amended claim 1 and page 6, lines 10-16), a feature absent in both Cruickshank et al. and Aebersold et al.

In particular, the specificity-determining ("S"-)part ensures that the compound is brought in close contact with its interaction partner, in such a way that the linking "L"-

part is transferred at a specific site of a specifically targeted partner. See e.g. following passages of the application:

> "Due to this interaction, the complete compound is brought in close contact with the target allowing the linking being established at reasonable concentrations of the compound. It is well known that increasing concentrations of the compound will decrease the specificity. Thus the"S"-part of the compound should interact with its target under physiologically relevant concentrations." See page 7, lines 1-5 of the present application.

> "This is illustrated in example 1.4 where the"S"-part and "L"-part contact different surfaces at the target protein. Such chemically reactive group can be a photo-activatable group such as a diazoketone, arylazide, arylketone, arylmethylhalide, etc. any of which can bind non- selectively to a target protein, but which is transferred by the"S"-part at a specific site of the target protein." See page 7, lines 21-25 of the present application.

Note that the "L"-part of the compound in the present invention is analogous to the protein reactive group described in Aebersold et al., but that the reagents of Aebersold lack the essential "S"-part to direct specificity – see the passages describing the "L"-part and protein reactive group respectively:

> "Such chemically reactive group can consist of a functional group with higher selectivity. Selectivity for amino-groups such as amidates, succinic acid anhydride and the like; for SH-groups such as methylmaleimide or acetylhalides and the like." See page 7, lines 25-27, of the present specification, emphasis added.

> "Examples of selectively reactive PRGs suitable for use in the affinity tagged reagents of this invention, include those which react with sulfhydryl groups to tag proteins containing cysteine, those that react with amino groups, carboxylate groups, ester groups, phosphate reactive groups, and

> aldehyde and/or ketone reactive groups or, after fragmentation with CNBr, with homoserine lactone." See Aebersold, column 10, lines 37-43, emphasis added.

It inherently follows that the use of the term 'selectively reactive' in the Aebersold patent differs from the term 'specificity-determining'. Thus, while the PRG of Aebersold et al. (or, for that matter, FDNB in Cruickshank et al.) may selectively interact with all proteins carrying a particular amino acid residue, this does not result in specificity. Indeed, this is just a manner of reducing the complexity of the mixture while still interacting with one peptide of each protein (and thus with all components present in the original mixture). See for example, the following passages of Aebersold et al.:

> "At least one peptide sequence derived from a protein will be characteristic of that protein and be indicative of its presence in the mixture. Thus, the sequences of the peptides typically provide sufficient information to identify one or more proteins present in a mixture." (column 5, lines 55-60)

> "For example, a theoretical tryptic digest of the entire yeast proteome (6113 proteins) produces 344,855 peptides, but only 30,619 of these peptides contain a cysteinyl residue. Thus, the complexity of the mixture is reduced, while protein quantitation and identification are still achieved." (column 15, lines 61-66)

It is exactly the presence of the specificity-determining part that ensures specific interaction partners can be identified, i.e. only a very specific subset of the proteins with which the "L"-part normally would be able to react (see application passages quoted above). It was very surprising, and a contribution of the present inventors, that it is possible to combine a specificity-determining part and a non-specific linking part in a compound while retaining specificity, even in complex mixtures.

Again, a person of skill in the art, when combining Cruickshank et al. and Aebersold et al. would not have been taught, suggested or motivated by either reference apart or in combination to use compounds with both a specificity-determining and linking part (in addition to the alterable part), and would thus not have arrived at the claimed invention. On the contrary, one of ordinary skill in the art is taught by Aebersold that, to achieve protein quantitation and identification, interaction with one peptide from each protein is desired. There is no indication in Cruickshank or Aebersold to adapt the methods for interaction partner identification (such as e.g. drug target identification). It is submitted that neither of these references, nor their combination would have rendered the presently claimed invention obvious. This is true for the independent claim and for the claims dependent therefrom.

The further combination with Johansson et al. was made only with regard to the features of dependent claims 6 and 7. As Johansson also does not teach or suggest the novel and inventive features of claim 1 (such as complex samples and the specific compounds listed in claim 1), claims 6 and 7, dependent on claim 1, are also novel and inventive over the combination of Cruickshank et al., Aebersold et al. and Johansson et al. the claims are patentable over the art of record.

As for the Examiner's reliance on the combination of Creighton et al. in view of Aebersold et al., the rejection is believed to be similar to the rejection over Cruickshank and Aebersold in that the Office Action asserts that Creighton teaches diagonal techniques for the purification of a protein in two chromatographic steps with an intervening modification step, while Aebersold allegedly teaches mass spectrometry-

based analysis of complex mixtures of proteins. Again, the applicants submit that the ordinarily skilled person would not have combined these two references when searching for a solution to the problem of interaction partner identification, and even if he had combined them, this combination would not have resulted in the instantly claimed invention.

Creighton, as described above, does not relate to isolation of specific interaction partners of a compound, does not teach complex mixtures and fails to disclose a compound having a specificity-determining part in addition to a linking and alteration part.

Aebersold et al., as discussed above, does not relate to interaction partner isolation (e.g. drug target identification) and does not disclose compounds having a specificity-determining part in addition to a linking and alteration part, allowing the isolation of one or a limited number of specific interaction partners.

Thus, even if an ordinarily skilled person would have combined the Creighton and Aebersold references and even if, only for the sake of the argument herein, this would have led him to use a complex mixture instead of the single protein taught by Creighton, this would not have resulted in the instantly claimed invention. Similarly as for the Cruickshank-Aebersold combination, neither Creighton nor Aebersold, alone or in combination, teach or suggest a method for interaction partner identification or the use of a compound with three distinct functionalities (among which a specificity-determining and linking part). As previously submitted, the applicants believe Aebersold et al. even teach away from the instantly claimed invention in stressing that every

protein should ideally be represented by at least one peptide (thus interaction should be with more peptides, not with less, but specific peptides as in the present invention). Consequently, the combination of Creighton and Aebersold et al. would not have rendered the claimed invention obvious for the same reasons that the combination of Cruickshank et al. and Aebersold et al. would not have rendered the claimed invention obvious.

The claims are submitted to be patentable over the cited combinations of art. Entry of the present Amendment and withdrawal of the Section 103 rejections are requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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